

Oral Mucositis Prevention and Management by Therapeutic Laser in Head and Neck Cancers

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Abstract:

Introduction: Oral mucositis is considered a severe complication in cancer patients receiving radiotherapy or chemotherapy for head and neck cancer. The aim of this review study was to assess the effect of low level laser therapy for prevention and management of oral mucositis in cancer patients.

Methods: The electronic databases searched included Pubmed, ISI Web of Knowledge and Google scholar with keywords as “oral mucositis”, “low level laser therapy” from 2000 to 2013.

Results: The results of most studies showed that photobiomodulation (PBM) reduced the severity of mucositis. Also, it can delay the appearance of severe mucositis.

Conclusion: Low level laser therapy is a safe approach for management and prevention of oral mucositis.

Keywords: low level laser therapy; mucositis; prevention; management.

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Introduction

Oral mucositis is considered as a painful condition in patients with cancer after radiotherapy and chemotherapy. It appears as small patches to big ulceration and hemorrhage in oral mucosa ¹.

The prevalence of mucositis is 40-100% dependent on the type cancer and therapy used. In 40% of chemotherapy patients and in 100 % of radiotherapy treated patients, mucositis happened ^{2, 3}.

Oral mucositis not only damages the epithelial cells but also the local tissue reaction causes damage from reactive oxygen species and inflammatory cytokines which finally results in submucosal tissue damage. Oral mucositis appears in oral mucosa after the 5th to 10th day after chemotherapy or radiotherapy. It manifests as a burning sensation to ulcer formation that affect the quality of life of patients by producing pain and discomfort for

swallowing which ultimately leads to malnutrition and dehydration ⁴.

Treatment modalities can be non-pharmacological and by pharmacological agents like lidocaine, morphine which is used as palliative care and pain relief. Non pharmacological treatments include mouthrinse, cryotherapy, etc ⁵. Recently, photobiomodulation has been used in different aspects of dentistry. photobiomodulation (PBM) is a safe, non pharmacological method which can modulate various metabolic processes via absorption of energy by chromophores ⁶.

Low level laser therapy changes the mitochondrial respiration and leads to increased ATP production which produces intracellular reactive oxygen species (ROS). These changes result in fibroblast proliferation, collagen synthesis, adjustment of inflammatory response, as well as motivation of angiogenesis and tissue repair ⁷.

There are several explanations for pain reduction

caused by PBM including modulation of the inflammatory process, alteration of excitation and nerve conduction in peripheral nerves and stimulation of release of endogenous endorphins⁸. So, laser therapy can be considered as a palliative treatment for this problem.

The aim of this review study was to assess the effect of low level laser therapy for prevention and management of oral mucositis in cancer patients.

Methods

The electronic databases searched included Pubmed, ISI Web of Knowledge and Google scholar with keywords as “oral mucositis”, “low level laser therapy” from 2000

to 2013.

The papers which are relevant were included in this review of literature.

74 articles were found, but 27 of them were selected for evaluation due to accessibility to their full texts. Also, systematic reviews and meta analysis were excluded.

Results

Among the 27 articles assessed, three of them were animal studies and 24 were human studies. The studies are summarized in Table 1 and Table 2. The results of most studies showed that PBM reduced the severity of mucositis. Also, it can delay the appearance of severe

Table 1. Human studies which evaluated the effect of low level laser therapy on management of oral mucositis.

| First author/ year | Title | participants | wavelength | Parameters | Results | Final |
|-------------------------------------|---|---|-----------------|---|---|-------|
| Antunes HS 2013 ⁹ | Phase III trial of low-level laser therapy to prevent oral mucositis in head and neck cancer patients treated with concurrent chemoradiation | 94 HNSCC patients | InGaAlP 660nm | P:100mW E:1J Energy density: 4J/cm ² | Preventive Low-level laser therapy (LLLT) in HNSCC patients receiving chemoradiotherapy is an effective tool for reducing the incidence of grade 3-4 oral mucositis (OM). | + |
| Arbabi-Kalati F 2013 ¹⁰ | Evaluation of the effect of low level laser on prevention of chemotherapy-induced mucositis | 24 HNC patients | Diode 630 nm | output power: 30 mW. energy dose : 5 J/cm ² | means of pain severity and mucositis grades were significantly lower in the case group compared to the control group | + |
| Gautam AP 2013 ¹¹ | Effect of low-level laser therapy on patient reported measures of oral mucositis and quality of life in head and neck cancer patients receiving chemoradiotherapy--a randomized controlled trial. | 220 HNC patients | He-Ne, 632.8 nm | power density = 24 mW/cm(2), dosage = 3.0 J at each point, total dose/ session = 36-40 J, spot size 1 cm(2), irradiation time/point 125 s) | LLLT was effective in improving the patient's subjective experience of OM and quality of life (QOL) in HNC patients receiving chemoradiotherapy. | + |
| Gautam AP 2012 ¹¹ | Low level laser therapy for concurrent chemoradiotherapy induced oral mucositis in head and neck cancer patients - a triple blinded randomized controlled trial | 221 HNC patients | HeNe, 632.8 nm | Power density=24 mW, dosage=3.0 J/ point, total dosage/ session=36-40 J, spot-size=1 cm(2), 5 sessions/week) | LLLT decreased the incidence of chemoradiotherapy induced severe OM and its associated pain, dysphagia and opioid analgesics use. | + |
| Hodgson BD 2012 ¹² | Amelioration of oral mucositis pain by NASA near-infrared light-emitting diodes in bone marrow transplant patients. | 80 HSCT patients | GaAlAs 670 nm | for 80 s at ~50 mW/cm(2) energy density : 4 J/cm(2). | Phototherapy demonstrated a significant reduction in patient-reported pain as measured by the WHO criteria in this patient population included in this study. | + |
| Gouvêa de Lima A 2012 ¹³ | Oral mucositis prevention by low-level laser therapy in head-and-neck cancer patients undergoing concurrent chemoradiotherapy: a phase III randomized study. | 75 HNSCC patients | GaAlAs | Energy density:2.5 J/cm(2) | LLL therapy was not effective in reducing severe oral mucositis, although a marginal benefit could not be excluded. | = |
| Carvalho PA, 2011 ¹⁴ | Evaluation of low-level laser therapy in the prevention and treatment of radiation-induced mucositis: a double-blind randomized study in head and neck cancer patients. | 70 patients with malignant neoplasms in the oral cavity or oropharynx | 660nm | Group 1: (15mW/3.8J/cm(2)/spot size 4mm(2)) Group 2: (660nm/5mW/1.3J/cm(2)/spot size 4mm(2)) | Low-level laser therapy during radiotherapy was found to be effective in controlling the intensity of mucositis and pain. | + |

Treatment of Oral Mucositis by Laser

Table 1. Continue

| | | | | | | |
|--|--|--|---|---|--|---|
| Cauwels RG 2011 ¹⁵ | Low level laser therapy in oral mucositis: a pilot study. | 16 children | GaAlAs 830 nm | Power: 150 mW. | Immediate pain relief and improved wound healing resolved functional impairment that was obtained in all cases. | + |
| Silva GB 2011 ¹⁶ | The prevention of induced oral mucositis with low-level laser therapy in bone marrow transplantation patients: a randomized clinical trial. | 42 HSCT patients | InGaAlP 660 nm | Power: 40 mW, Energy density: 4 J/cm | Our results indicate that the preventive use of LLLT in patients who have undergone HSCT is a powerful instrument in reducing OM incidence. | + |
| Lima AG 2010 ¹⁷ | Efficacy of low-level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy-induced oral mucositis. | 25 HNC patients | 830 nm | Twelve patients received LLLT (15 mW, 12 J/cm ²) daily from the 1st day until the end of RT before each sessions during 5 consecutive days | The prophylactic use of both treatments proposed in this study seems to reduce the incidence of severe OM lesions. However, the LLLT was more effective in delaying the appearance of severe OM. | + |
| Khoury VY 2009 ¹⁸ | Use of therapeutic laser for prevention and treatment of oral mucositis. | 22 HSCT patients | InGaAlP 660 nm GaAlAs 780 nm | Power: 25 mW dose: 6.3J/cm ² 10 s | Laser reduced the frequency and severity of oral mucositis. | + |
| Zanin T, 2010 ¹⁹ | Use of 660-nm diode laser in the prevention and treatment of human oral mucositis induced by radiotherapy and chemotherapy. | 72 patients HNC patients | diode 660 nm | Power : 30 mW, spot size = 2 mm, energy = 2 J per point | Laser therapy was effective in preventing and treating oral effects induced by radiotherapy and chemotherapy, thus improving the patient's quality of life. | + |
| Simões A, 2009 ²⁰ | Laser phototherapy as topical prophylaxis against head and neck cancer radiotherapy-induced oral mucositis: comparison between low and high/low power lasers. | 39 HNC patients | InGaAlP laser (660 nm) GaAlAs laser (808 nm) | LPT: 40 mW/6Jcm ⁻² /0.24 J per point). high power LPT : 1 W/cm ² . | Low-intensity laser therapy appears to reduce the severity of mucositis, at least in part, by reducing cyclooxygenase-2 levels and associated inhibition of the inflammatory response. | + |
| Kuhn A 2009 ²¹ | Low-level infrared laser therapy in chemotherapy-induced oral mucositis: a randomized placebo-controlled trial in children. | 21 patients (86%) patients had a diagnosis of leukemia or lymphoma and 3(14%) had solid tumors | GaAlAs 830 nm | Power: 100 mW, dose: 4 J/cm ² , | laser therapy in addition to oral care can decrease the duration of chemotherapy-induced OM. | + |
| Campos L, 2009 ²² | Improvement in quality of life of an oncological patient by laser phototherapy. | a 15-year-old girl diagnosed | Diode 660 nm | Power: 40 mW, energy density: 6 J/cm ² , 0.24 J per point, spot size of 0.04 cm ² A high-power diode laser at 1 W, 10 J/cm ² defocused mode | Normal oral function and consequent improvements in the quality of life of this oncologic patient were observed with laser phototherapy (LPT). | + |
| Eduardo FP 2009 ²³ | Severity of oral mucositis in patients undergoing hematopoietic cell transplantation and an oral laser phototherapy protocol: a survey of 30 patients. | 30 patients undergoing HCT | Diode 660 nm | Power: 40 mW | The low grades of OM observed in this survey show the beneficial effects of laser phototherapy. | + |
| Abramoff MM 2008 ²⁴ | Low-level laser therapy in the prevention and treatment of chemotherapy-induced oral mucositis in young patients. | 13 Patients | GaAlAs 685 nm | Power: 35 mW 600-m spot. energy: 2 J per point, dose: 72 J/cm ² . | The ease of use of LLLT, high patient acceptance, and the positive results achieved, make this therapy feasible for the prevention and treatment of OM in young patients. | + |
| Genot-Klastersky MT 2008 ²⁵ | The use of low-energy laser (LEL) for the prevention of chemotherapy- and/or radiotherapy-induced oral mucositis in cancer patients: results from two prospective studies. | First study: 26 patients Second study: 36 patients | Visible IR | visible 100 mW laser and an IR laser with power from 50, 250, and 500 mW | LEL is an effective and safe approach to prevent or treat oral mucositis resulting from cancer chemotherapy. | + |

Treatment of Oral Mucositis by Laser

Table 1. Continue

| | | | | | | |
|---------------------------------|--|---|-------------------|--|--|---|
| Antunes HS 2008 ²⁶ | The Impact of low power laser in the treatment of conditioning-induced oral mucositis: a report of 11 clinical cases and their review. | 11 HSCT patients | InGaAlP, 660 nm | Power: 50 mW dose: 8 J/cm ² | The use of low power laser therapy in HSCT patients is a powerful instrument in the treatment of overt oral mucositis. | + |
| Arora H 2008 ²⁷ | Efficacy of He-Ne Laser in the prevention and treatment of radiotherapy-induced oral mucositis in oral cancer patients. | 24 HNC patients | He-Ne 632.8nm | Power: 10 mW energy density: 1.8 J/cm ² . | Laser therapy applied prophylactically during radiotherapy can reduce the severity of oral mucositis, severity of pain, and functional impairment. | + |
| Jaguar GC 2007 ²⁹ | Low-energy laser therapy for prevention of oral mucositis in hematopoietic stem cell transplantation. | 24 HSCT patients | GaAlAs 660 nm | power :10 mW energy density: 2,5 J/cm ² | This study suggests that laser therapy can be useful in oral mucositis to HSCT patients and improve the patient's quality of life. | + |
| Schubert MM 2007 ⁵ | A phase III randomized double-blind placebo-controlled clinical trial to determine the efficacy of low level laser therapy for the prevention of oral mucositis in patients undergoing hematopoietic cell transplantation. | 70 HCT patients | 650 nm 780 nm | energy density: 2 J/cm ² . | LLLT reduced the severity of oral mucositis and pain scores | + |
| Cruz LB 2007 ²⁹ | Influence of low-energy laser in the prevention of oral mucositis in children with cancer receiving chemotherapy. | 60 HSCT patients | 780 nm wavelength | Power: 60mW, Dose: 4 J/cm ² . | This study showed no evidence of benefit from the prophylactic use of low-energy laser in children and adolescents with cancer treated with chemotherapy when optimal dental and oral care was provided. | = |
| Arun Maiya G 2006 ³⁰ | Effect of low level helium-neon (He-Ne) laser therapy in the prevention & treatment of radiation induced mucositis in head & neck cancer patients | 20 patients with carcinoma of oral cavity with stages II-IV | He-Ne 632.8 nm | Power: 10mW | The low-level He-Ne laser therapy during the radiotherapy treatment was found to be effective in preventing and treating the mucositis in head and neck cancer patients. | + |
| Nes AG 2005 ³¹ | Patients with moderate chemotherapy-induced mucositis: pain therapy using low intensity lasers. | 13 adult patients | AsGaAl 830 nm | Power: 250 mW. Dose: 35 J cm ⁻² . | There was a significant decrease in the daily average experience of pain felt before and after each treatment. | + |

Table 2. Animal studies which evaluated the effect of low level laser therapy on management of oral mucositis.

| Author/ year | Title | participants | wavelength | Parameters | Results | Final |
|-----------------------------|---|------------------|----------------|--|---|-------|
| Lopes NN 2010 ³² | Effects of low-level laser therapy on collagen expression and neutrophil infiltrate in 5-fluorouracil-induced oral mucositis in hamsters. | 72 hamster cheek | InGaAlP 660 nm | power of 35 or 100 mW | LLLT promotes wound healing and appears to have an anti-inflammatory effect, as evidenced by the reduction in neutrophil infiltrate. | + |
| Lopes NN 2009 ³³ | Cyclooxygenase-2 and vascular endothelial growth factor expression in 5-fluorouracil-induced oral mucositis in hamsters: evaluation of two low-intensity laser protocols. | 72 hamster cheek | InGaAlP 660 nm | Power: 35 mW or 100 mW laser | The increase in collagen organization in response to the 35 mW laser indicates that LLLT promotes wound healing. Also, LLLT also appears to have an anti-inflammatory effect. | + |
| França CM 2009 ⁴ | Low-intensity red laser on the prevention and treatment of induced-oral mucositis in hamsters. | 30 hamsters | Diode 660 nm | Power= 30mW, Dose=1.2J/cm ² , 40s, spot size 3mm ² , | The results suggest that laser phototherapy had a positive effect in reducing mucositis severity, and a more pronounced effect in treating established mucositis. | + |

HNSCC: head and neck squamous cell carcinoma

HNC: head and neck cancer

HSCT: hematopoietic stem cell transplant

GaAlAs: gallium-aluminum-arsenide

InGaAlP: Indium Gallium Aluminum Phosphorus

+: effective response

=: no effective response

mucositis.

Discussion

Oral mucositis is considered as a side effect of radiotherapy or chemotherapy of head and neck cancer patients.

It's necessary to standardize some protocols for prevention and management of chemotherapy or radiotherapy induced oral mucositis to prevent reduction or discontinuation of treatments²⁰. Recently, researches have focused on the effects of low level laser therapy as a new modality for managing this problem via photobiomodulation effect^{9, 10}. Oral mucositis exhibit different biologic phases including initiation, inflammatory response, amplification/ signaling, ulceration and healing. Acceleration of wound healing happens through enhanced release of growth factors, increased neovascularization and collagen formation. Some studies stated that laser can increase the production of vascular endothelial growth factor (VEGF) which results in angiogenesis and improved microcirculation and subsequently to wound healing^{33, 34}.

Mostly, low level laser therapy was performed by diode lasers including red and infra-red wavelengths. Shorter wavelengths (632.8-660 nm) can affect the superficial layer of the epithelium but longer wavelengths penetrate deeper and affect sub-epithelial tissues. It seems that shorter wavelengths are more effective than longer ones in treatment of oral mucositis which was approved by Schubert et al. Red laser are absorbed in superficial layer of oral mucosa which is favorable for wound healing⁵.

The effect of laser on oral mucositis showed some beneficial effects such as it delayed the time of onset, reduced the peak severity and shortened the duration of this problem. These advantages can be attributed to anti-inflammatory and analgesic effects of laser which are followed by increased local vascularity and re-epithelization of tissue³⁰. Oral wound healing can be achieved by transformation of fibroblast to myofibroblasts which promote mucosal healing. On the other hand, analgesic effects can happen through release of endorphin and ekephalin. The other mechanism of laser induced pain relief is through membrane cell depolarization, blocking the nervous impulse and fast axonal flow³⁵.

Most of studies showed the positive effect of PBM on oral mucositis but there were just two studies that reported negative effect of laser therapy. Curz et al. in assessing low level laser therapy in prevention of oral mucositis in children came to this conclusion that low level laser therapy had no beneficial effect as prophylactic option for prevention of oral mucositis²⁹.

Bjordal et al. conducted meta-analysis of the effect of

Low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis. Despite, various laser wavelengths, parameters and dosage, they demonstrated moderate to strong evidence for efficacy of LLLT in oral mucositis management³⁵. Also, Migliorati et al. stated that LLLT can become a routine practice in management of oral mucositis to control its severity³⁶.

In assessing animal studies, anti-inflammatory effect of LLLT and wound healing was seen due to reduction in neutrophil infiltrate and cyclooxygenase-2 expression^{32, 33}.

Other factors such as oral hygiene had influenced on prevention of oral mucositis. So, patients should be educated about oral hygiene and given instructions. Some researchers showed positive effects of good oral health on reducing the risk of severe mucositis due to decrease of oral bacteria²⁹.

One of the main factors that can enhance the prevention of oral mucositis is the ideal time of starting laser therapy which has not been clear and needs clinical trials which would evaluate and compare the different startpoints of treatment to clarify it³⁵.

According to two meta-analysis conducted about laser phototherapy in management of oral mucositis in head and neck cancers, LLLT can be used with doses of 1-6 J per point in oropharyngeal area by existence of moderate to strong evidence. For radiotherapy induced oral mucositis, a suggestion of laser therapy was possible with wavelength of 632 nm. No guideline was possible for application of LLL in management of oral mucositis in patients treated with a combined protocol of radiochemotherapy for head and neck cancer. Also, there was no possible guideline for chemotherapy induced oral mucositis due to low level of evidence^{35, 36}.

Several studies showed positive results of LLLT for reducing the incidence and severity of mucositis accompanied by other advantages such as improved quality of life of patients. More standard investigations are needed to clarify which parameters including wavelength, energy density, time of exposure, have the best interactions with tissues to produce favorable outcomes.

Conclusion

Low level laser therapy is a noninvasive modality for prevention and management of oral mucositis with to some advantages like analgesic effect, inflammation reduction and atraumatic repeated use.

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